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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/438,358	11/12/99	GERARD G	0942.4640001

HM22/1001
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EXAMINER	
LEFFERS JR, G	
ART UNIT	**PAPER NUMBER**
1636	13

DATE MAILED: 10/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/438,358	Applicant(s) GERARD ET AL.	
	Examiner Gerlad Leffers	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-51 and 65-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-51 and 65-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Rita Adams

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of supplemental information disclosure statements (IDS) filed 3/8/01 and 4/9/01 as Paper No. 10 and Paper No. 11, respectively. The corresponding PTO Form 1449 for each has been mailed with this action.

Receipt is acknowledged of applicants' amendment, filed 3/8/01 as Paper No. 12, in which the nonelected claims were cancelled (claims 1-13, 52-64), several claims were amended (14-15, 1929, 31-33, 37-40, 50) and new claims were added (claims 65-88). Claims 14-51 and 65-88 are pending and under consideration in this application.

Any rejection of record in Paper No. 8 not addressed in this action has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-39, 65-79, 81-83, 85-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **The following rejections are maintained for reasons of record in Paper No. 8, mailed 11/8/00 and repeated below. The rejections are extended to newly added claims 65-79, 81-83 and 85-87.**

Claims 14 and 19 are vague and indefinite in that the metes and bounds of the term "effective amount" of a ribosomal protein are unclear. **This rejection is extended to amended claim 31.** How much of a ribosomal protein constitutes and effective amount when it is added to a recombination reaction? It would be remedial to amend the claim language to clearly indicate

what constitutes an "effective amount" of a ribosomal protein when it comes to recombination of nucleic acids.

Response to Arguments

Applicant's arguments filed in Paper No. 12 have been fully considered but they are not persuasive. Applicants' response points to several lines from the specification as clearly defining the metes and bounds of the term "effective amount" as applied to ribosomal proteins in the context of the invention (page 33, lines 3-23). The response further argues enablement with regard to determination of such "effective amounts" of ribosomal proteins. These arguments are unpersuasive in that the cited passages in no way provide a clear definition as to what constitutes an effective amount of a ribosomal protein in the context of recombination of nucleic acids. For example, the cited passage on page 33 of the specification recites several broad ranges of some recombination proteins which may be effective in the methods of the claimed invention. Such broad, prophetic teachings do not make clear the metes and bounds of the claimed invention. The arguments regarding enablement of the claimed invention are not relevant to the instant rejection under 35 U.S.C. 112, second paragraph, and do not make clear the metes and bounds of the claimed invention.

Claims 14 and 19 are also vague and indefinite in that the metes and bounds of the term "do not substantially recombine" are unclear. The term does not appear to be well defined in the specification and is inherently indefinite. Would a single instance of recombination constitute "substantial" recombination? Would 5 instances of recombination between the two sites constitute "substantial recombination"? Exactly what frequency of recombination between the

sites would constitute "substantial recombination"? It would be remedial to amend the claim language to clearly indicate what is intended by the limitation of no "substantial" recombination.

Response to Arguments

Applicant's arguments filed in Paper No. 12 have been fully considered but they are not persuasive. Applicants' response essentially argues that the specification and prior art present data to indicate that different combinations of recombination sites will be recombined at different frequencies. The question remains, however, what degree of recombination between the different recombination sites is to be considered as the minimal level to constitute "substantial" recombination? Applicants' response and the prior art provide no answer to this question.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 36, 38-51, 65-72, 74-76, 79-80, 87-88 are rejected under 35 U.S.C. 102(b) as being anticipated by Nash (Methods in Enzymology. Vol. 100, pp210-216, see the entire reference). **This rejection is maintained for reasons of record in Paper No. 8, mailed 11/8/00. This rejection is extended to new claims 65-72, 74-76, 79-80 and 87-88.**

It is noted that Nash teaches the "isolation" of ribosomal and recombinase proteins to varying degrees for use in the recombination reaction mixtures throughout the reference. Nash

also teaches the recombinant expression of the recombinase Int (e.g. pages 212-213, *Purification*).

Claims 40-51, 80 and 88 are rejected under 35 U.S.C. 102(b) as being anticipated by Abremski et al (V; The Journal of Biological Chemistry, Vol. 259, No. 3, pages 1509-1514; see the entire reference) and Abremski et al (W; The Journal of Biological Chemistry. Vol. 257, No. 16, pages 9658-9662; see the entire reference). **This rejection is maintained for reasons of record in Paper No. 8, mailed 11/8/00 and extended to newly added claims 80 and 88.**

It is noted both references teach the "isolation" of ribosomal and recombinase proteins to varying degrees for use in recombination reaction mixtures. Both references teach the recombinant expression of recombinase proteins.

Response to Arguments

Applicant's arguments filed in Paper No. 12 have been fully considered but they are not persuasive. Applicants' response to each of the rejections made under 35 U.S.C. 102(b) as being anticipated by Nash, Abremski et al or Abremski et al is that the cited references do not teach each and every limitation of the claimed invention (i.e. the presence of ribosomal proteins in the crude extracts added to recombination mixtures). The response alleges that the arguments for inherency presented by the examiner in Paper No. 8 regarding the presence of ribosomal proteins in the crude extracts used in each of the cited references during characterization of an isolated recombinase are inadequate. It is asserted that for none of the cited references does the reference

indicate that the ribosomal proteins are necessarily present in the crude extracts. This assertion is inaccurate.

For example, the Nash et al reference teaches that the crude E. coli cell extracts utilized for characterization of the λ int recombinase were generated by lysis of the cell wall/membrane by sonication and centrifugation at 15,000 RPM for 20 minutes to pellet the insoluble debris (e.g. page 212, second full paragraph, *Preparation of crude IHF*). Both of the Abremski et al references teach lysis of E. coli cells by sonication and centrifugation at 17,000 RPM for 30 minutes to generate crude extracts which were assayed for recombinase activity (e.g. see each results section under *Enzyme Purification*). Such cell lysis and centrifugation techniques are and were routinely practiced in the art and are recognized as providing an E. coli cell extract comprising isolated and soluble proteins, including ribosomal polypeptides. For example, Robyt and White teach that a centrifugal force of up to 100,000g for 3-10 hours is required to sediment ribosomal proteins (Table 8-2; *Biochemical Techniques-Theories and Practice*, John F. Robyt and Bernard J. White, 1987, Brooks-Cole publishers, Monteray CA). The examiner knows of no commonly used centrifuge rotor that will generate these kinds of centrifugal forces at the speeds indicated by the supporting references.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-51, 65-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al in view of Nash (U) or Abremski et al (V) or Abremski et al(W). **This rejection is maintained for reasons of record in Paper No. 8. This rejection is extended to newly added claims 65-80.**

Response to Arguments

Applicant's arguments filed in Paper No. 12 have been fully considered but they are not persuasive. Applicants' response essentially argues: 1) Hartley et al do not disclose each of the claim limitations, 2) the examiner appears to rely on an inherency argument for Hartley et al with regard to the presence of ribosomal proteins, 3) there is no such thing as "inherent obviousness" since inherence and obviousness are different legal concepts, 4) the deficiencies of Hartley et al are not cured by the supporting references because the references do not explicitly teach the addition of ribosomal proteins in their methods, 5) there is no motivation to combine the teachings of the different references and no expectation of success.

At no point in making the rejection of the instant claims as being obvious over Hartley et al in view of Nash, Abremski et al or Abremski et al did the examiner indicate that Hartley et al necessarily teaches the use of crude extracts comprising ribosomal proteins for recombination of DNA substrates in vitro. There was no argument presented in the instant rejection with regard to an inherent teaching from the Hartley et al reference. The examiner did point out that the in vitro methods taught by Hartley et al do encompass in vitro embodiments wherein the recombination enzymes are supplied as part of a crude cellular extract following overexpression in bacterial cells. Hartley et al teach each of the other limitations present in the rejected claims (e.g. site specific recombinases used to recombine Insert Donors, Vector donors, etc.). The supporting references cited in the instant rejection provide teachings to indicate that one can practice such methods with crude cellular extracts in order to provide the recombinase proteins along with other cellular factors which can aid recombination (e.g. IHF for Int or Xis mediated recombination).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation for combining the teachings of the primary and secondary references is to receive the expected benefit of providing one or more recombination proteins to the in vitro recombination mixture without the need for further purifying of recombination elements and, in

the case of Int/Xis, providing multiple factors known to enhance recombination (e.g. IHF). Applicants' response does not address this motivation directly and does not provide a rational argument or evidence to support its assertion that there would have been no expectation of success in practicing the methods taught by Hartley et al with crude cellular extracts as taught in the supporting references.

As indicated above, in terms of motivation to combine references there is no need for a specific teaching in the supporting references that ribosomal proteins are necessarily present in the crude extracts taught by the supporting references because this is not the basis for combining the references. The supporting references are applicable, however, with regard to the presence of ribosomal proteins in the recombination mixtures of the invention because such ribosomal proteins would necessarily be present in the crude extracts taught by the supporting references. For example, the Nash reference teaches that the crude E. coli cell extracts utilized for characterization of the λ int recombinase were generated by lysis of the cell wall/membrane by sonication and centrifugation at 15,000 RPM for 20 minutes to pellet the insoluble debris (e.g. page 212, second full paragraph, *Preparation of crude IHF*). Both of the Abremski et al references teach lysis of E. coli cells by sonication and centrifugation at 17,000 RPM for 30 minutes to generate crude extracts which were assayed for recombinase activity (e.g. see each results section under *Enzyme Purification*). Such cell lysis and centrifugation techniques are and were routinely practiced in the art and are recognized as providing an E. coli cell extract comprising isolated and soluble proteins, including ribosomal polypeptides. For example, Robyt and White teach that a centrifugal force of up to 100,000g for 3-10 hours is required to sediment ribosomal proteins (Table 8-2; *Biochemical Techniques-Theories and Practice*, John F. Robyt

and Bernard J. White, 1987, Brooks-Cole publishers, Monteray CA). The examiner knows of no commonly used centrifuge rotor that will generate these kinds of centrifugal forces at the speeds indicated by the supporting references.

Arguments along the lines of there being no specific teaching in the supporting references regarding addition of ribosomal proteins to the recombination mixture appear to be arguing a limitation which is not actually present in the claims. The claims use open claim language (e.g. A method...comprising:...) and do not actually link the recombination of substrate DNA molecules to the presence of ribosomal proteins. The claims merely state that ribosomal proteins are present in the reaction mixture without directly linking them to the recombination events. The term "an effective amount" of ribosomal proteins is not clearly defined in the specification and does not serve the purpose of linking the presence of such ribosomal proteins to recombination efficiency. Thus, the motivation to combine the teachings of the primary reference and secondary references does not need to rely upon a functional contribution of the ribosomal proteins.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-51, 65-88 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37 of U.S. Patent No. 5,888,732. Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons of record in Paper No. 8. **This rejection is maintained for reasons of record in Paper No. 8 and extended to newly added claims 65-80.**

Response to Arguments

Applicant's arguments filed in Paper No. 12 have been fully considered but they are not persuasive. Applicants' response argues that the Hartley et al reference does not necessarily teach the addition of ribosomal proteins to recombination reaction mixtures and that the rejection be held in abeyance until such time as allowable subject matter is indicated. Rejection of the instant claims as not being patentable over the claims of the '732 patent was not based upon any inherency argument with regard to the '732 patent. The rejection was based upon the fact that the claims embrace in vitro embodiments wherein a crude cellular extract is used to provide recombination proteins and/or other factors to the recombination mixture and that such extracts would necessarily comprise ribosomal proteins (see above). As applicants' response has not obviated the grounds for the instant rejection, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers , Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Rob Schwartzman, Ph.D., can be reached at (703) 308-7307.

Any inquiry of a general nature or relating to the status of this application, or relating to attachments to this office action, should be directed to the Patent Analyst Zeta Adams, whose telephone number is (703) 305-3291.

DD2

G. Leffers Jr., Ph.D.
Patent Examiner
Art Unit 1636
13 July 2001

DAVID GUZO
PRIMARY EXAMINER